

DIFFICULT ASTHMA – 3 CASE REPORTS

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INTRODUCTION

Asthma treatment is guided by assessment of asthma control. Guidelines specify a stepwise approach to escalating asthma treatment for uncontrolled asthma. Prior to changing treatment, however, doctors should ensure that the diagnosis is correct, that there is no ongoing exposure to potential allergic or non-allergic triggers and that adherence and technique have been optimised. If the asthma is still uncontrolled, exacerbating conditions and comorbid diseases should be sought. The three cases below illustrate some of the factors that can complicate the management of 'difficult' asthma.

CASE 1

Patient ZR is a 5-year-old boy who was referred to the tertiary allergy clinic with uncontrolled asthma.

Background

He is a black African, with no significant background history. His first presentation was of episodic viral wheeze and then multitrigger wheeze. He was commenced on inhaled corticosteroids (ICS) at age 4, and a leukotriene-receptor antagonist (LTRA) was added because of ongoing poor control.

On assessment at the allergy clinic, his weight and height plotted on the 25th centile. His peak expiratory flow (PEF) was 80% expected. He had evidence of allergic facies and allergic rhinoconjunctivitis on examination. His chest was hyperinflated and had wheezes bilaterally.

Skin-prick tests (SPTs) for aeroallergen sensitisation were positive for house-dust mite and grass mix. Immunoglobulin levels were normal, excluding immunodeficiency, and a sweat test excluded cystic fibrosis. He was on budesonide 200 µg twice daily, and intranasal beclomethasone for comorbid allergic rhinitis. His technique of metered-dose inhaler (MDI) was suboptimal, but his adherence impeccable. The management on his initial visit was to increase his ICS and demonstrate correct MDI technique.

On subsequent visits his PEF was 70-80% expected and significant symptoms were still present despite the changes to his medication technique. He had multiple visits for nebulisations to the community health centre and had received multiple short courses of prednisone. A chest X-ray (CXR), pulmonary function tests and blood tests for possible allergic bronchopulmonary aspergillosis (ABPA) were done.

Special investigations

- CXR showed hyperinflation but no significant infiltrates

- Total IgE 1 540 kU/l
- IgE *Aspergillus* 0.82 kU/l
- IgG *Aspergillus* 35.8 mg/l.

A diagnosis of poorly controlled asthma exacerbated by ABPA was made. He was commenced on combination long-acting beta-2-agonist (LABA) and ICS, and high-dose prednisone for ABPA.

CASE 2

Patient NW is a 7-year-old girl who presented to medical casualty with worsening asthma control. Her PEF was 39% of expected and she was treated for a life-threatening asthma exacerbation. She had attended peripheral hospitals and had been on amoxycillin and then co-amoxycylav. She was changed to azithromycin to cover for infection with an atypical organism. A nasopharyngeal aspirate (NPA) was requested to exclude a viral trigger and she was discharged after 5 days in hospital.

Her maintenance medicines were salmeterol/fluticasone 25/250 µg twice daily, and montelukast 5 mg at night.

On review at the allergy clinic her PEF was 91% expected, but her asthma was still uncontrolled despite 2 weeks of prednisone. The result from the NPA done during her recent admission was negative for viruses. Based on the severity of symptoms and difficulty controlling patient NW, a thorough review of her medical records was performed.

Background

Her background was of episodic viral wheeze in the first year of life that responded to bronchodilators. She was commenced on ICS at the age of 7 months and was thought to be an early asthmatic. At the age of 15 months she was referred to the tertiary allergy clinic for assessment, and had bilateral grommet insertion for chronic otitis media with effusion later that year. For the following 3 years she was seen regularly at the allergy clinic with a history of requiring reliever treatment regularly and often complaining of an irritating cough. Additional problems were recurrent ear infections and constipation requiring regular medication.

At the beginning of 2007 she had adenotonsillectomy and reinsertion of her grommets. Between 2007 and 2009 multiple changes to her medication did not substantially improve asthma control. At age 4 LABAs were added to ICS therapy. SPTs showed sensitisation to house-dust mite, grass mix and dog. For the following year her asthma remained uncontrolled and the LABA dose was doubled.

Because of her recent admission, and based on the severity of her symptoms and lack of control, a workup was commenced for exacerbators or possible alternative diagnoses.

Special investigations

- Immunoglobulin A, G, M within normal range
- Total IgE 232 kU/l
- IgE *Aspergillus* was negative

- Milk scan negative for reflux
- Sputum was negative on direct microscopy and culture for tuberculosis
- Pulmonary function tests are shown in Table I
- Sweat test chloride of 73 and then 86 (range 40-60 suspicious; >60 indicative of cystic fibrosis)
- Subsequent DNA studies were sent for the specific genetic defect and confirmed homozygosity 3272-26A→G.
- Stool elastase was >500 which confirmed normal exocrine pancreatic function, and explained her normal growth parameters.

A diagnosis of cystic fibrosis with superadded reversible lower airway obstruction was made and she was transferred to a subspecialist cystic fibrosis clinic.

Table I. Pulmonary function tests – case 2

Measurement	Pred	Pre	% Pred	Post	% Pred	% Diff
FVC (l)	2.03	1.46	72	1.71	84	17
FEV ₁ (l)	1.98	1.39	70	1.55	79	12
FEV ₁ %FVC (%)	86.00	95.01	110	90.93	106	-4
FEF25 (l/s)	3.80	2.24	59	2.79	74	25
FEF50 (l/s)	2.68	1.53	57	1.60	60	5
FEF75 (l/s)	1.37	0.85	62	0.77	56	-10
PEF (l/s)	4.79	3.02	63	3.74	78	24

Pred – predicted; Diff – difference; FVC – forced vital capacity; FEV₁ – forced expiratory volume in 1 second; FEF – forced expiratory flow; PEF – peak expiratory flow.

Table II. Pulmonary function tests – case 3

Measurement	Pred	Pre	% Pred	Post	% Pred	% Diff
FVC (l)	1.93	2.19	113	2.18	113	0
FEV ₁ (l)	1.88	1.40	75	1.53	81	9
FEV ₁ %FVC (%)	86.00	63.85	74	69.9	81	10
FEF25 (l/s)	3.65	1.64	45	2.22	61	19
FEF50 (l/s)	2.57	0.89	35	1.24	48	36
FEF75 (l/s)	1.32	0.35	27	0.47	36	34
PEF (l/s)	4.57	2.77	61	3.31	72	19

Pred – predicted; Diff – difference; FVC – forced vital capacity; FEV₁ – forced expiratory volume in 1 second; FEF – forced expiratory flow; PEF – peak expiratory flow.

CASE 3

Patient SD is a 10-year-old girl referred to the tertiary allergy clinic for difficult-to-control asthma. Her maintenance medication was budesonide 400 µg twice daily with formoterol 24 µg twice daily and montelukast 5 mg daily. Her asthma was uncontrolled on these medications. Her adherence and technique were impeccable after extensive counselling, and she was monosensitive to house-dust mite.

Background

As a neonate she had severe laryngomalacia requiring laryngeal trimming and had subsequent feeding problems and severe gastro-oesophageal reflux demonstrated on barium swallow. This was followed up by the dietician and thought to have resolved.

She had multitrigger wheeze in the first year of life and was commenced on ICS at the age of 14 months. Her parents defaulted follow-up and after 4 years she returned with a severe exacerbation. She was recommenced on budesonide 200 µg twice daily as well as treatment for allergic rhinoconjunctivitis and atopic dermatitis.

Over the next 3 years her PEF was consistently 55-70% expected, and her parents were counselled for non-adherence. Her therapy was stepped up to high-dose budesonide and montelukast as add-on therapy.

Special investigations

- Milk scan
 - Residual buccal activity was seen throughout the study
 - Fourteen episodes of reflux during the 30-minute observation, with many reaching beyond the cervical level
- Total IgE 3 872 kU/l
- IgE *Aspergillus* 13.8 kU/l
- IgG *Aspergillus* 25.3 mg/l

- Peripheral eosinophil count 0.98 x 10⁹ (15%)
- Exhaled nitric oxide (FeNO) 50 ppb
- Pulmonary function tests (Table II).

A diagnosis of poorly controlled asthma exacerbated by severe reflux and ABPA was made. She was commenced on a proton-pump inhibitor, treatment for ABPA and changed to combination LABA/ICS.

Follow-up

At follow-up a month later, her PEF was 76% predicted, and her FeNO was down to 20 ppb. A modified barium swallow was booked to exclude laryngeal entry and micro-aspiration, and repeat IgE was done to monitor response to treatment. Her blood results indicated a good response to ABPA therapy as follows:

- IgE 1 962 kU/l
- IgE *Aspergillus* 9.29 kU/l
- IgG *Aspergillus* 8.1 mg/l.

The modified barium swallow showed no laryngeal entry and a normal pharyngeal trigger to swallowing, but showed persistent reflux to above the clavicles. At the following visit her PEF was 86% predicted

but unfortunately she had rebound of symptoms on weaning the prednisone. Her FeNO had increased again to 50 ppb and her 6-minute walk test showed moderate impairment.

She was maintained on low-dose prednisone, and voriconazole was added to treat the ABPA. She has been discussed with our surgical colleagues for an antireflux procedure and is due to be reviewed by the pulmonology division for a computed tomography (CT) scan of the chest.

DISCUSSION

Severe asthma has multiple synonyms and definitions. A recent WHO definition^{1,2} proposes a simple and uniform way to classify difficult asthma.

- **Untreated asthma.** Asthma may be untreated because the diagnosis has not been made, or basic medication is not available or affordable. Exacerbators can complicate this, such as environmental tobacco smoke exposure, biomass exposure, untreated allergic rhinosinusitis or gastro-oesophageal reflux disease (GORD).

- The second category is **difficult-to-treat asthma**. These patients have asthma but have poor response to treatment because of non-adherence, incorrect technique for inhalations or inappropriate device choice and education of the patient.
- The last category is **treatment-resistant asthma** and these children are on maximal medical therapy. However the definition of maximal medical therapy may depend on which medications are routinely available. In South African primary and secondary health care, these children would be on budesonide 800 µg per day in addition to theophylline to control their asthma, whereas in specialised tertiary hospital clinics maximal medical therapy may be combination LABA/ICS with the addition of an LTRA.¹

With all cases of 'difficult' asthma, the diagnosis should be reviewed to ensure that the correct diagnosis has been made. The differential diagnosis of asthma in children over the age of 5 years is provided in Table III.^{3,4}

Table III. Differential diagnosis of asthma^{4,5}

Tuberculosis
Foreign body
Bronchiectasis
Chronic obstructive airways disease (post viral/lung damage post ventilation including lung disease of prematurity)
Aspiration syndromes
Cystic fibrosis
Tracheal/bronchial compression syndromes
Allergic bronchopulmonary aspergillosis
Vocal cord dysfunction
Congestive cardiac failure

In order to confirm the diagnosis of asthma, the clinician should ensure that the child in question has recurrent, reversible peripheral airways obstruction that responds to bronchodilators. This is confirmed by history, a modified (bedside) bronchodilator response test in young children, and wherever possible confirmed with lung function tests showing a >12% change in forced expiratory volume in 1 second (FEV1) or a >20% change in PEF after the administration of a beta-2-agonist or a >20% diurnal variation in PEF. In some children a response to anti-inflammatory asthma therapy is the only way to confirm the diagnosis.

Adherence should be checked with open-ended questions, the use of asthma diaries, and devices with dose counters where available. Technique should be directly assessed at all visits with the patient demonstrating the use of their device rather than simply describing it. The appropriateness of devices should be regularly reviewed with the changing age and capabilities of the child.

If the doctor is satisfied that the diagnosis, adherence and technique are satisfactory but the asthma remains uncontrolled, exacerbators should be sought to explain the loss of control, or inability to control the asthma (Table IV).⁴

GORD with aspiration can be the primary diagnosis in a patient with peripheral airways obstruction, but can also be as a result of the medication and disease, or just a comorbidity in asthma. This is detected with a suggestive history, barium swallow or scintigraphy. The gold standard for diagnosis of GOR is a pH study with manometry.

Table IV. Exacerbators of asthma⁵

Rhinosinusitis
GORD
Ongoing allergen exposure
Allergic bronchopulmonary aspergillosis
Obstructive sleep apnoea
Medications – aspirin, NSAIDs, beta-blockers, ACE-inhibitors and oestrogens
Psychosocial factors
History of psychiatric disease
GORD – gastro-oesophageal reflux disease; NSAIDs – non-steroidal anti-inflammatory drugs; ACE – angiotensin-converting enzyme.

Cystic fibrosis is an important differential diagnosis with early-onset wheeze. Cystic fibrosis may occur in children with normal growth if there is pancreatic sufficiency. Cystic fibrosis may coexist with asthma. The gold standard for diagnosis is sweat conductivity or electrolyte testing.

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disorder to the mould *Aspergillus fumigatus*, and occurs mainly in patients with asthma or cystic fibrosis. There are set diagnostic criteria, but it may be difficult to differentiate true ABPA from sensitisation to *Aspergillus*. The use of recombinant allergens may differentiate between the two.⁵

Aspergillus sensitisation in asthma is 40% with the prevalence of ABPA 12.9%.⁶ In the cases presented, recombinant allergen tests were not done, but the patients were treated as if they had ABPA. Azoles for ABPA have shown a synergistic role with prednisone for the treatment of the condition. Azoles significantly decrease the amount and number of courses of prednisone required to control asthma and allow cessation of prednisone in 60% of cases. Azoles also significantly improve pulmonary function tests and allow asthma severity to be downgraded from severe to moderate.^{7,8}

Declaration of conflict of interest

The authors declare no conflict of interest.

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ASTHMA AND ALLERGY

RESEARCH GRANT

As a further commitment to providing quality medical care to all South Africans, Cipla Medpro has granted an amount of R25 000 to the Allergy Society of South Africa for research in the field of asthma and allergic rhinitis.

Applications will be considered for research projects relating to asthma and allergic rhinitis, whether basic or applied; however conventional drug trials will not be acceptable.

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